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# Bacterial infections in anorexia nervosa:

# Delayed recognition increases complications

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BACTERIAL INFECTIONS IN ANOREXIA NERVOSA

**Abstract**

**Objective:** We compared the natural history of bacterial infection in anorexia nervosa (AN) with controls, and assessed which of a range of patient characteristics were associated with infection, fever response, and the rate of infectious complications in AN. **Method:** The charts of 311 consecutive hospital admissions of AN patients were reviewed. Cases who had a bacterial infection while in hospital were compared to the remainder, with respect to a range of demographic and disease variables. Fever response and infection complication rate were also evaluated in AN infection-cases and non-anorectic control subjects admitted with a bacterial infection. **Results:** Anorectic bacterial infection-cases showed a reduced fever response, were often difficult to diagnose because of fewer signs and symptoms, and infection became more frequent with increasing patient age. **Conclusions:** A reduction in fever response and the signs and symptoms of infection significantly delayed diagnosis in AN patients and increased the complication rate from bacterial infection. We recommend that an increased index of suspicion and an early complete blood count and bacteriological cultures be adopted for the investigation of bacterial infection in AN.

Keywords: anorexia nervosa, bacterial infection, fever

Bacterial infections in anorexia nervosa: Delayed recognition increases complications

The incidence of viral and bacterial infection is not increased in anorexia nervosa (AN) (Berkman, 1948; Bowers & Eckert, 1978), although the morbidity (Devuyst, Lambert, Rodhain, Lefebvre & Coche, 1993) and mortality (Theander, 1970; Warren & Vander Weile, 1973) associated with bacterial infections are. The fever response to bacterial infection is often decreased in AN patients (Birmingham et al., 2003; Marcos, 2000; van Rijn, 1998) and this may contribute to infectious disease complications. Basal hypothermia is common in AN (Bock, 1993; Okamoto et al. 1991), and body temperatures are commonly less than 35.5 degrees C (Palla & Litt, 1988).

These are not, however, wholly consistent results. Luck & Wakeling (1982) failed to detect any difference in the core body temperatures of AN patients and controls, but did find higher thermal preferences in AN patients. Moreover, a significant fever response up to 39.7 degrees C is described in one AN patient with multiple serious bacterial infections (Hoffman, Herzum & Maisch, 1994), and in one patient with no apparent infection (Fukudo et al., 1993).

In our recent small case series, all AN patients during the course of a bacterial infection presented with temperatures less than 37 degrees C (Birmingham et al., 2003). This is consistent with the clinical observation of a reduced or absent fever response (Marcos, 2000; van Rijn, 1998) and a reduced leukocytic response (van Rijn, 1998) to bacterial infection in AN. Failure to mount a detectable fever response to exogenous bacterial pyrogen administration has also been reported in one AN patient (Frankel & Jenkins, 1975). One report also suggests that the ability to develop fever during hospitalisation is a sign of significant improvement in AN (Marcos, 2000).

Fever is a highly adaptive response that, together with immune responses, can facilitate recovery from infectious disease. This recovery appears to be facilitated by (i) an array of innate and adaptive immune responses and (ii) the suppression of viral and bacterial growth by body temperatures that are above the optimal temperature range of the infectious agent (Mackowiak, Marling-Cason & Cohen, 1982; Mackowiak & Marling-Cason, 1983). AN patients often present with a range of immune disturbances including usually mild leukopenia and anemia (Mant & Faragher, 1972; Warren & Vande Wiele, 1973) and less common thrombocytopenia (Devuyst et al., 1993).

A reduced or absent fever response to bacterial infection may also contribute to the development of infectious disease complications in AN. However, little is known about the relationship between these and other clinical variables (e.g. leukocyte count), although AN infection-cases are reported to have an increased rate of infectious complications (Copeland & Herzog, 1987; Devuyst et al., 1993).

The aim of this retrospective medical record audit was to more fully describe the natural history of infectious disease in AN. We were particularly interested in the fever response to bacterial infection and risk factors for the development of bacterial infection in AN. On the basis of the literature, we hypothesized that: AN patients who were diagnosed with a bacterial infection would show: (i) a non-detectable fever response relative to non-infected AN patients (non-cases); (ii) a reduced fever response to bacterial infection relative to non-anorectic infection controls (infection-controls); and (iii) an increased presence and number of infectious disease complications compared to non-anorectic infection controls. We also examined the possible risk factors for the development of a bacterial infection in AN.

## METHODS

This retrospective medical record audit study was conducted with human research ethics committee approval. We examined the records of 311 consecutive patients admitted to Royal Prince Alfred Hospital, Sydney, Australia, from 1 January 1992 to 31

December 2002. The following data were collected from the medical records of all AN patients: age (years), sex, years since AN diagnosis, AN subtype (restricting, purging, other), concurrent illness (e.g. refeeding syndrome, depression), number of admissions since AN diagnosis, duration of admission (days), reason for admission (infection, treatment of eating disorder, other), weight (kg), height (m) and body mass index (BMI) at admission, and discharge status (alive/dead).

AN patient admissions were categorized as either an 'infection-cases' or 'non-cases', on the basis of a thorough inspection of the medical records. Infection-cases were AN patients admitted for the treatment of a suspected bacterial infection, or when a bacterial infection was diagnosed during an admission for another reason. Detailed temperature data was collected on all infection-cases, from the onset of bacterial infection until discharge. Admission day temperatures were also collected on all AN non-cases, and were compared to infection-case temperature data: either (a) admission day temperatures in patients diagnosed at admission with a bacterial infection; or (b) day-of-diagnosis temperature data in patients diagnosed with later infection. Relevant clinical data were also collected on all infection-cases, including diagnosis, investigation and treatment of infection, co-morbid disease and infectious disease complications.

Each infection-case was matched to a general medical admission patient who had a bacterial infection, on the basis of age, sex, site of infection, and when specified, the infective organism. Whenever possible, we collected detailed temperature and relevant clinical data (as described above) on matched controls.

**Statistical Analysis**

Data analysis was conducted using SPSS (Version 11.5). Two-tailed tests with a $p = 0.05$ were taken as significant for all statistical tests. None of the continuous data were normally distributed except for height. The Mann-Whitney U test was therefore used to compare continuous variables including age, admission temperature, BMI, weight, years since diagnosis and duration of admission. Studentized t-tests were used to compare height between AN infection-cases and non-cases. Chi-square analyses were used to compare AN-cases and non-cases on all categorical variables including sex, AN type and reason for admission.

A single binary logistic regression for the outcome of bacterial infection (yes/no) was also conducted. A range of variables were permitted to compete for inclusion in the regression models, based on their association with the bacterial infection outcome variable. Correlations were reported as Pearson product moment correlations *r* (two-tailed) for the relationship between bacterial infection to all continuous variables. All statistically significant covariates were included in the model including age, body temperature and reason for admission. AN-subtype was included as a possible confounder in this analysis. Results were reported in terms of the Wald statistic, odds ratios (OR) and 95% confidence intervals (95% CI).

Limited comparisons were made between AN infection-cases and non-anorectic infection controls. The Mann-Whitney U test was used to compare fever response ($^{o}$C), number of infectious disease complications, age and duration of admission. Chi-square analyses were used to compare sex, and occurrence of infectious disease complications.

## RESULTS

### Participants

The records of 311 consecutive admissions were searched; medical records for two AN patients could not be located. Twenty-three AN patients were documented as bacterial infection-cases (7%); the remaining 288 were non-cases. Six patients (2%) were given a primary diagnosis of viral infection and seven (2%) were given prophylactic antibiotics after a traumatic injury. There were similar numbers of infection-cases in all the years searched.

Infection-cases

Of the 23 infection-cases, 16 (70%) presented with serious infections. Five patients presented with pneumonia, five with urinary tract infections (UTI), three with cellulitis, two with a foot infection and one with quinsy. Of the seven patients with non-serious infections, three presented with helicobacter pylori gut infection, two with simple vaginal infections, and one each with conjunctivitis and folliculitis.

The fever response of all but five infection-cases was below 37$^{o}$C, and some were as low as 35.5 $^{o}$C. Five cases (22%) mounted a detectable fever response ranging from 37.5 - 39.5 $^{o}$C. These patients all had serious infections (i.e. cellulitis, quinsy, UTI), a swinging pyrexia and appeared more debilitated than other infection-cases (e.g. polydrug users). However, most of the serious bacterial infection-cases in this study did not mount a detectable fever response, and unexplained fevers (37.6 - 38.2 $^{o}$C) were detected in two of the 6 patients with probable viral infections.

The infectious disease course was complex in some AN patients, although no patients died during their hospital admission. For example, two patients (9%) had dual infection diagnoses at presentation; one had both a pneumonia and a UTI, and one had pneumonia followed by an infected central line. There was also a high rate of co-morbid disease in AN infection-cases, including psychiatric and physical diagnoses. For example, infection-cases were commonly dehydrated and had a range of metabolic disorders including hypokalemia, hyponatremia and hypoglycemia. They often had osteopenia/ osteoporosis, anemia or were depressed, and some showed additional metabolic derangements (e.g. low serum calcium, iron, magnesium, phosphate or zinc), delirium or obsessive-compulsive traits. Some infection-cases were also polydrug users (e.g. heroin, alcohol) and had viral hepatitis. Only one infection-case presented with the refeeding syndrome.

Some infection-cases presented with occult disease or symptoms that were difficult to diagnose on admission. For example, four patients (17%) presented to hospital either unconscious or in collapse. Two of five pneumonia patients presented with occult disease; one for the investigation of weight loss, delirium and weakness, and one with unexplained fevers and weight loss. Two of the five UTI patients also presented with co-morbid disease; one with delirium and the other with unexplained edema, rapid weight increase and hypoproteinemia.

Bacteriological cultures and full blood counts were often not performed on infection-cases, although there was a trend towards high white cell counts, with increased neutophils and low lymphocyte counts in infection-cases. Standard antibiotic regimens were administered to infection-cases, and all patients initially responded normally to antibiotic treatment.

Comparison of infection-cases & non-cases

Infection-cases were older (29.3 yrs) than non-cases (25.1 yrs; $z = -2.51$, $p=0.01$). Reason for admission also differed between cases and non-cases ($X_2^2 = 52.88$, $p=0.00$), with infection-cases more often admitted for infection (26%) than non-cases (1%), and less often admitted for the treatment of their eating disorder (43%) than non-cases (65%). No other significant differences were detected between cases and non-cases: infection-cases had similar body temperatures to non-cases (Figure 1) and similar weights, BMI, number of previous admissions, duration of admission and time since AN diagnosis (see Table 1). Infection-cases were also equally likely to be female (96%) compared to non-cases (96%; $X_1^2 = 0.00$, $p=0.97$), and anorexia subtype differences were not detected between cases and non-cases ($X_2^2 = 2.29$, $p=0.32$).

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Figure 1 about here

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Table 1 about here

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We tested a binary logistic regression model for the outcome of bacterial infection. Bacterial infections were poorly but significantly correlated with higher age (r=0.14, p=0.01) and higher body temperature (r=0.19, p=0.006). The model was significant and included age, body temperature, reason for admission and AN-subtype (Wald $X_1^2 = 92.04$, p=0.00). Age (OR=1.11; 95%CI, 1.03 - 1.18) and infection as the reason for admission (OR=45.56; 95%CI, 4.96 – 418.66) were the only variables significantly related to bacterial infection in AN patients. Body temperature failed to predict bacterial infection occurrence in AN infection-cases (OR=0.94; 95%CI, 0.40 - 2.17). Thus, AN patients with a bacterial infection were older and more likely to be admitted with an infectious diagnosis than non-cases, although infection-caseness was not predicted by a detectable fever response (Table 2).

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Table 2 about here

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Comparison of infection-cases & infection-controls

Infection-cases were the same age as non-anorectic infection-controls (29.3 vs. 29.8 yrs; z = -0.24, p=0.81) and were matched on the basis of sex ($X_1^2$=0.00, p=1.00), site of infection and infective diagnosis. A mean of 2-years (max. 4 yrs) separated the time of diagnosis for matched infection-cases and infection-controls, increasing the likelihood they received similar infection treatment protocols.

AN infection-cases showed a smaller fever response (36.7 °C) than non-anorectic infection-controls (37.1 °C; z=-1.96, p=0.05). They were more likely to develop infectious disease complications than infection-controls ($X_1^2 = 12.51$, p=0.00), and experienced more infectious disease complications (mean = 1.5) than non-anorectic infection-controls (mean = 0.2, z=-3.44, p=0.00). They also spent much longer in hospital (47.9 days) than non-anorectic infection-controls (5.7 days, z=-4.60, p=0.00).

## DISCUSSION

Over an 11-year period 311 AN patients were admitted to hospital, of which 23 had a bacterial infection that either resulted in the admission or occurred during it. Older patients more often developed a bacterial infection, especially if they were in poor physical condition. However, no other clinical or demographic variables, including body temperature could predict bacterial infection occurrence in AN patients.

AN infection-cases generally had no fever. Most had temperatures below 37°C and some were as low as 35.5 °C, and only a non-significant 0.5°C temperature difference was detected between AN infection-cases and non-cases. The temperatures of infection-cases were also significantly lower (36.7 °C) than those of non-anorectic infection-controls (37.1 °C).

Infection-cases who did mount a detectable fever response had more serious bacterial infections, although most cases with a serious bacterial infection did not mount a fever response. Detectable fever responses were not limited to serious bacterial infections; unexplained fevers were also detected in non-cases with probable viral infections. These observations are consistent with reports of both a reduced fever response (Birmingham et al., 2003; Marcos, 2000) and normal fever response (Hoffman et al., 1994; Fukudo et al., 1993) in AN infection-cases.

AN patients were likely to have experienced a delay in their infection diagnosis because: (a) most infection-cases failed to mount a detectable fever, (b) approximately one-third were unconscious or collapsed on admission, and (c) many had symptoms that were absent or difficult to diagnose. This is reflected in the high rates of admission for reasons other than infection in AN infection-cases. Thus, alternative methods of investigation (e.g. full blood count) are required for AN patients with a suspected bacterial infection. Full blood counts, however, were rarely performed as part of the general work-up for infection-cases in this study, although some patients showed high white cell counts, detectable neutrophil responses and low lymphocyte counts.

Most infection-cases presented with serious bacterial infections. They were more likely to develop infectious disease complications (e.g. renal failure, readmission for treatment of infection) than non-anorectic infection-controls, and they spent a longer time in hospital and experienced more infectious disease complications. Cases were also commonly dehydrated and had high rates of co-morbid psychiatric illness and poor physical condition including anemia, osteoporosis, metabolic derangements, substance use and depression. These observations are consistent with reports in the clinical literature of increased morbidity associated with infection (Copeland & Herzog, 1987; Devuyst et al., 1993). However, infection-cases did not have lower BMI, longer hospitalisations, longer times since AN diagnosis nor more previous hospital admissions than AN non-cases, suggesting that infection-cases were not obviously more debilitated than AN non-cases.

These data must be interpreted with caution given the study's obvious limitations. This study was a retrospective audit study, so missing or partial data could not easily be verified by the attending clinicians. Second, mild bacterial infection rates were likely to have been underestimated in AN patients, since patients were more likely to have consulted their GP than attended hospital for treatment.

In summary, older AN patients were more likely to have developed a bacterial infection than younger patients. Most bacterial infection-cases did not develop a detectable fever response. Many also had difficult to diagnose or occult disease symptoms, and many developed infectious disease complications. At present, there are no recommendations for special prophylaxis, monitoring, early treatment or special treatment of bacterial infections in AN. We recommend that an increased index of suspicion and an early complete blood count and bacteriological cultures be adopted for the investigation of suspected bacterial infection in AN.

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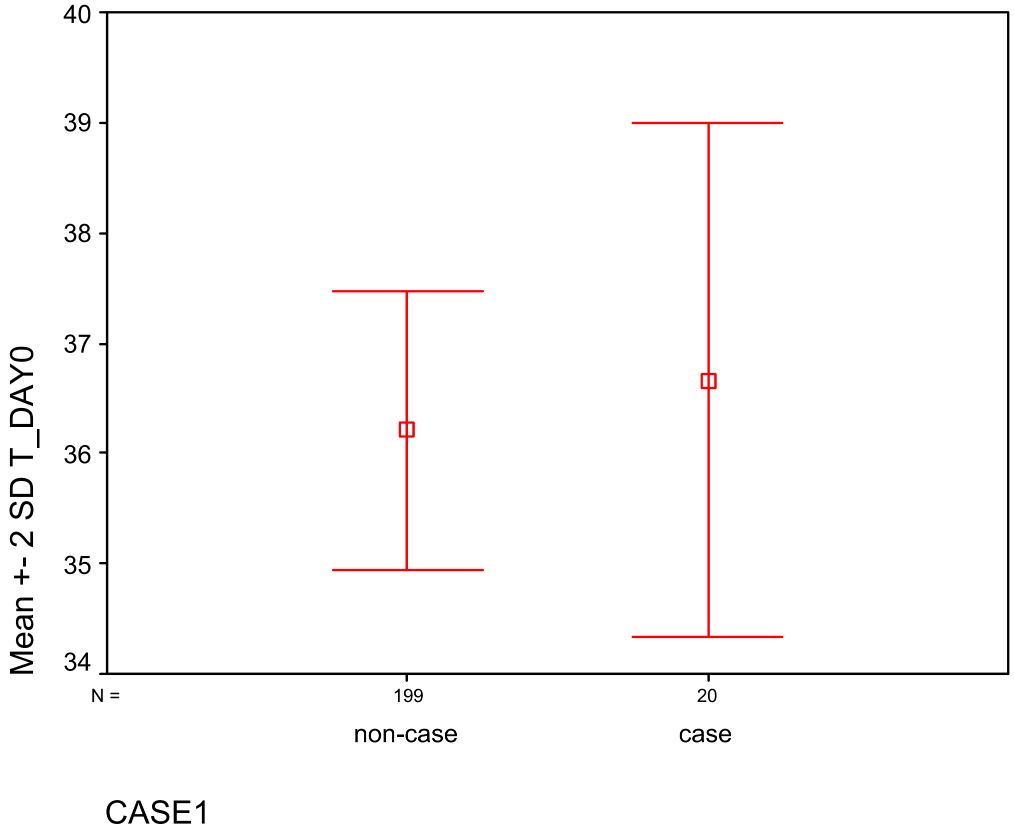


Figure 1

Body temperature data in anorexia nervosa infection-cases and non-cases ($T^oC$)

Table 1

Differences in mean clinical measures between anorexia nervosa infection-cases and non-cases

| | Infection-cases | Non-cases | Z-value | Sig (p) |
|---|---|---|---|---|
| Age (years) | 29.3 | 25.1 | -2.51 | 0.01* |
| Temperature ($^{o}$C) | 36.7 | 36.2 | -0.81 | 0.42 |
| Weight (kg) | 40.5 | 42.7 | -0.53 | 0.60 |
| BMI | 15.0 | 15.9 | -1.12 | 0.26 |
| Years since diag | 7.6 | 5.3 | -1.35 | 0.18 |
| No. adms | 1.7 | 1.5 | -1.32 | 0.19 |
| Duration adms | 47.9 | 38.4 | -0.93 | 0.35 |

Table 2

Predictors of bacterial infection-caseness in anorexia nervosa patients

| | Odds ratio | Confidence interval |
|---|---|---|
| Age | 1.11 | 1.03 - 1.18 |
| Reason admission | 45.56 | 4.96 – 418.66 |
| T°C | 0.94 | 0.40 - 2.17 |
| AN-type | 1.21 | 0.22 – 6.53 |